

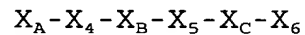
**Amendments to the Claim:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1-17 (cancelled).

18 (currently amended). A non-naturally occurring polypeptide, or a polypeptide in at least partially purified form, which is six to 20 amino acids in length, and which comprises the following sequence



wherein  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu, Val, norvaline, norleucine, methionine-S-oxide, N-methylvaline, N-methyl isoleucine, allo-leucine, and their D-isomers;

$X_6$  is selected from the group consisting of Asn, Asp, Gln, Glu, and their D-isomers,

$X_A$  is L-Thr or D-Thr,

$X_B$  is L-Lys, L-Orn, L-Dab, or one of their D-isomers, and

$X_C$  is L-Arg or D-Arg,

wherein at least one of the following conditions (I)-(V) is true;

I) at least one of  $X_A$ ,  $X_B$ ,  $X_C$ ,  $X_4$ ,  $X_5$  or  $X_6$  is a non-natural or unusual amino acid,

II) the polypeptide is cyclized,

III) the polypeptide is stabilized,

IV) the aminoterminal amino acid residue is acylated, or

V) the carboxyterminal amino acid residue is amidated,

~~where, if the polypeptide is not cyclized, said sequence corresponds essentially to the C-terminal of said polypeptide,~~  
said polypeptide having at least one of the following properties:

a) induces inhibition of spontaneous IL-8 production by human monocytes,

b) induces inhibition of IL-1 $\beta$  induced IL-8 production by

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human peripheral blood mononuclear cells (PBMC),

c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,

d) induces chemotactic migration of CD8+ human T lymphocytes in vitro,

e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,

f) suppresses the chemotactic response of CD4+ T human lymphocytes towards IL-8,

g) suppresses the chemotactic response of human monocytes towards MCAF/MCP-1,

h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- $\gamma$ ,

i) induces the production of IL-4 by cultured normal human CD4+ T cells,

j) reduces TNF $\alpha$  production in human mixed leukocyte reaction, or

k) downregulates TNF $\alpha$  and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits.

19 (previously presented). A polypeptide according to claim 18, which comprises the following sequence

$X_3$ -Thr- $X_4$ -Lys- $X_5$ -Arg- $X_6$  (SEQ ID NO:20),

wherein

$X_3$ ,  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu and Val; and

$X_6$  is selected from the group consisting of Asn, Asp, Gln and Glu,

wherein at least one of the following conditions (I)-(V) is true:

I) at least one of  $X_3$ ,  $X_4$ ,  $X_5$ ,  $X_6$ , Thr, Lys, and Arg is independently substituted with a non-natural or unusual amino acid,

II) the polypeptide is cyclized,

- III) the polypeptide is stabilized,
- IV) the aminoterminal amino acid residue is acylated, or
- V) the carboxyterminal amino acid residue is amidated.

20 (previously presented). A polypeptide according to claim 18, which comprises the following sequence

$X_2$ - $X_3$ -Thr- $X_4$ -Lys- $X_5$ -Arg- $X_6$  (SEQ ID NO:21),

wherein

$X_2$  is Tyr or Phe,

$X_3$ ,  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu and Val; and

$X_6$  is selected from the group consisting of Asn, Asp, Gln and Glu,

wherein at least one of the following conditions (I)-(V) is true:

I) at least one of  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$ ,  $X_6$ , Thr, Lys, and Arg is independently substituted with a non-natural or unusual amino acid,

II) the polypeptide is cyclized,

III) the polypeptide is stabilized,

IV) the aminoterminal amino acid residue is acylated, or

V) the carboxyterminal amino acid residue is amidated.

21 (previously presented). A polypeptide according to claim 18, which comprises the following sequence

$X_1$ - $X_2$ - $X_3$ -Thr- $X_4$ -Lys- $X_5$ -Arg- $X_6$  (SEQ ID NO:22),

wherein

$X_1$  is Ala or Gly,

$X_2$  is Tyr or Phe,

$X_3$ ,  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu and Val; and

$X_6$  is selected from the group consisting of Asn, Asp, Gln and Glu,

wherein at least one of the following conditions (I)-(V) is true:

I) at least one of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$ ,  $X_6$ , Thr, Lys, and Arg is independently substituted with a non-natural or unusual amino

acid,

II) the polypeptide is cyclized,

III) the polypeptide is stabilized,

IV) the aminoterminal amino acid residue is acylated, or

V) the carboxyterminal amino acid residue is amidated.

22 (currently amended). A polypeptide amounting to six to twenty amino acids which comprises the following sequence

Thr-X<sub>4</sub>-Lys-X<sub>5</sub>-Arg-X<sub>6</sub> (SEQ ID NO:19),

wherein

X<sub>4</sub> and X<sub>5</sub> are independently selected from the group consisting of Met, Ile, Leu and Val; and

X<sub>6</sub> is selected from the group consisting of Asn, Asp, Gln and Glu,

or which comprises a sequence which differs from SEQ ID NO:19 solely in that at least one of Thr, Lys, and Arg in SEQ ID NO:19 is independently substituted with a non-natural or unusual amino acid selected from the group consisting of ~~the amino acids of Reference Table A~~

<u>Aad</u>	<u>2-Aminoadipic acid</u>
<u>bAad</u>	<u>3-Aminoadipic acid</u>
<u>bAla</u>	<u>beta-Alanine, beta-Aminopropionic acid</u>
<u>Abu</u>	<u>2-Aminobutyric acid</u>
<u>4Abu</u>	<u>4-Aminobutyric acid, piperidinic acid</u>
<u>Acp</u>	<u>6-Aminocaproic acid</u>
<u>Ahe</u>	<u>2-Aminoheptanoic acid</u>
<u>Aib</u>	<u>2-Aminoisobutyric acid</u>
<u>bAib</u>	<u>3-Aminoisobutyric acid</u>
<u>Apm</u>	<u>2-Aminopimelic acid</u>
<u>Dbu</u>	<u>2,4-Diaminobutyric acid</u>
<u>Des</u>	<u>Desmosine</u>
<u>Dpm</u>	<u>2,2'-Diaminopimelic acid</u>
<u>Dpr</u>	<u>2,3-Diaminopropionic acid</u>
<u>EtGly</u>	<u>N-Ethylglycine</u>

<u>EtAsn</u>	<u>N-Ethylasparagine</u>
<u>Hyl</u>	<u>Hydroxylysine</u>
<u>aHyl</u>	<u>alo-Hydroxylysine</u>
<u>3Hyp</u>	<u>3-Hydroxyproline</u>
<u>4Hyp</u>	<u>4-Hydroxyproline</u>
<u>Ide</u>	<u>Isodesmosine</u>
<u>aIle</u>	<u>allo-Isoleucine</u>
<u>MeGly</u>	<u>N-Methylglycine, sarcosine</u>
<u>MeIle</u>	<u>N-Methylisoleucine</u>
<u>MeLys</u>	<u>6-N-Methyllysine</u>
<u>MeVal</u>	<u>N-Methylvaline</u>
<u>Nva</u>	<u>Norvaline</u>
<u>Nle</u>	<u>Norleucine</u>
<u>and</u>	
<u>Orn</u>	<u>Ornithine,</u>

said polypeptide having at least one of the properties defined in claim 18.

23-24 (cancelled).

25 (previously presented). A polypeptide according to claim 18 amounting up to 15 amino acids.

26 (previously presented). A polypeptide according to claim 18 amounting in total 10, 11, 12, 13, or 14 amino acids.

27 (previously presented). A polypeptide according to claim 18 amounting in total 9 amino acids.

28 (previously presented). The polypeptide of claim 21 wherein at least condition (I) is true.

29 (previously presented). The polypeptide of claim 20 wherein at least condition (I) is true.

30 (previously presented). The polypeptide of claim 19 wherein at least condition (I) is true.

31 (previously presented). The polypeptide of claim 18 wherein at least condition (I) is true.

32 (previously presented). The polypeptide of claim 18

which has the amino acid sequence Ala-Tyr-Met-Thr-Met-Lys-Ile-Arg-Asn (SEQ ID NO:1).

33 (previously presented). A substance which is a polypeptide as defined in claim 18 or is a salt, ester, or a solvate of said polypeptide.

34 (previously presented). A polypeptide according to claim 18 which is cyclized.

35 (previously presented). A polypeptide according to claim 18 which is stabilized.

36 (previously presented). A polypeptide according to claim 18 wherein the aminoterminal amino acid residue is acylated.

37 (previously presented). A polypeptide according to claim 18 wherein the carboxyterminal amino acid residue is amidated.

38 (previously presented). A polypeptide according to claim 18 encapsulated in a liposome.

39 (previously presented). A polypeptide according to claim 18 in substantially pure form.

40 (currently amended). A peptidomimetic modelled on the basis of a polypeptide according to claim 18, where said peptidomimetic comprises an alpha-helical template.

41 (previously presented). A pharmaceutical composition comprising a polypeptide according to claim 18, or a salt, ester or solvate of said polypeptide, or a peptidomimetic modelled on the basis of said polypeptide, where said peptidomimetic comprises an alpha helical template.

42-48 (cancelled).

49 (previously presented). A method of treating a disease which is treatable by a substance which has at least one of the following properties,

a) induces inhibition of spontaneous IL-8 production by human monocytes,

b) induces inhibition of IL-1 $\beta$  induced IL-8 production by human peripheral blood mononuclear cells (PBMC),

- c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,
- d) induces chemotactic migration of CD8+ human T lymphocytes in vitro,
- e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,
- f) suppresses the chemotactic response of CD4+ T human lymphocytes towards IL-8,
- g) suppresses the chemotactic response of human monocytes towards MCAF/MCP-1,
- h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- $\gamma$ ,
- i) induces the production of IL-4 by cultured normal human CD4+ T cells,
- j) reduces the TNF $\alpha$  production in human mixed leukocyte reaction, or
- k) downregulates TNF $\alpha$  and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits

which comprises administering to a subject in need thereof a pharmaceutically effective amount of a pharmaceutical composition according to claim 41.

... 50 (previously presented). A method of

- a) inducing inhibition of spontaneous IL-8 production by human monocytes,
- b) inducing inhibition of IL-1 $\beta$  induced IL-8 production by human peripheral blood mononuclear cells (PBMC),
- c) inducing production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,
- d) inducing chemotactic migration of CD8+ human T lymphocytes in vitro,
- e) desensitizing human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,

f) suppressing the chemotactic response of CD4+ T human lymphocytes towards IL-8,

g) suppressing the chemotactic response of human monocytes towards MCAF/MCP-1,

h) inhibiting class II MHC molecule expression on human monocytes stimulated by IFN- $\gamma$ ,

i) inducing the production of IL-4 by cultured normal human CD4+ T cells,

j) reducing the TNF $\alpha$  production in human mixed leukocyte reaction, or

k) downregulating TNF $\alpha$  and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits

which comprises administering to a subject an effective amount of a pharmaceutical composition according to claim 41.

51 (previously presented). The method of claim 49 wherein the disease is acute pancreatitis.

52 (previously presented). The method of claim 49 in which the disease is ARDS-like syndrome.

53 (previously presented). The method of claim 49 wherein acute pancreatitis is treated, resulting in prevention of ARDS-like syndrome.

54-56 (cancelled).

57 (previously presented). The method of claim 49 in which the disease is a cancer.

58 (cancelled).

59 (previously presented) The method of claim 49 in which the disease is an arthritis.

60 (cancelled).

61 (previously presented). The method of claim 49 in which the disease is a pancreatitis.

62 (cancelled).

63 (previously presented). The method of claim 49 in which



the disease is an ARDS-like syndrome.

64 (cancelled).

65 (previously presented). The polypeptide of claim 18 where SEQ ID NO:19 is the C-terminal of said polypeptide and the polypeptide is not cyclized.

66 (previously presented). The polypeptide of claim 65 which has a length of up to about 20 amino acids.

67 (previously presented). The polypeptide of claim 66 whose length does not exceed 10 amino acids.

68 (previously presented). The polypeptide of claim 18, said polypeptide being selected from the group consisting of polypeptides identical to SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, and SEQ ID NO:22, except that at least one of conditions (I)-(V) applies.

69 (cancelled).

70 (currently amended). The method of claim 49 ~~69~~ where the disease involves pro-inflammatory activities.

71 (currently amended). The method of claim 49 ~~69~~ where the disease is one inhibited by IL-10.

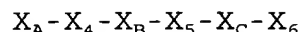
72 (currently amended). The method of claim 49 ~~69~~ where the disease is one caused or aggravated by IL-8, MCAF or IL-1.

73 (currently amended). The polypeptide of claim 18 where said amino acids each have a molecular weight not exceeding that of Fmoc-His(Trt)-OPfp ~~(785.78 daltons)~~.

74 (previously presented). The polypeptide of claim 18 where said amino acids, other than X<sub>A</sub>, X<sub>B</sub>, X<sub>C</sub>, X<sub>4</sub>, X<sub>5</sub> or X<sub>6</sub>, are alpha or beta amino acids.

75 (previously presented). The polypeptide of claim 18 which is not more than 15 a.a. in length.

76 (currently amended). A non-naturally occurring polypeptide, or a polypeptide in at least partially purified form, which is six to 20 amino acids in length, and which comprises the following sequence



$X_A$  is L-Thr or a non-natural or unusual amino acid,

$X_B$  is L-Lys or a non-natural or unusual amino acid,

$X_C$  is L-Arg or a non-natural or unusual amino acid,

$X_4$  and  $X_5$  are independently selected from the group consisting of L-Met, L-Ile, L-Leu, L-Val and a non-natural or unusual amino acid,

$X_6$  is L-Asn, L-Asp, L-Gln, L-Glu, or a non-naturally or unusual amino acid,

no more than one of  $X_A$ ,  $X_B$ ,  $X_C$ ,  $X_4$ ,  $X_5$  and  $X_6$  is a non-natural or unusual amino acid other than the D-isomer of an L-amino acid recited as possible at that position,

wherein at least one of the following conditions (I)-(V) is true:

I) at least one of  $X_A$ ,  $X_B$ ,  $X_C$ ,  $X_4$ ,  $X_5$  or  $X_6$  is a non-natural or unusual amino acid,

II) the polypeptide is cyclized,

III) the polypeptide is stabilized,

IV) the aminoterminal amino acid residue is acylated, or

V) the carboxyterminal amino acid residue is amidated,

~~where, if the polypeptide is not cyclized, said sequence corresponds essentially to the C-terminal of said polypeptide,~~  
said polypeptide having at least one of the following properties:

a) induces inhibition of spontaneous IL-8 production by human monocytes,

b) induces inhibition of IL-1 $\beta$  induced IL-8 production by human peripheral blood mononuclear cells (PBMC),

c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,

d) induces chemotactic migration of CD8+ human T lymphocytes in vitro,

e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,

f) suppresses the chemotactic response of CD4+ T human

lymphocytes towards IL-8,

g) suppresses the chemotactic response of human monocytes towards MCAF/MCP-1,

h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- $\gamma$ ,

i) induces the production of IL-4 by cultured normal human CD4+ T cells,

j) reduces TNF $\alpha$  production in human mixed leukocyte reaction, or

k) downregulates TNF $\alpha$  and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits, and wherein any non-natural or unusual amino acid referred to above is an amino acid ~~set forth in reference table A~~ selected from the group consisting of

<u>Aad</u>	<u>2-Aminoadipic acid</u>
<u>bAad</u>	<u>3-Aminoadipic acid</u>
<u>bAla</u>	<u>beta-Alanine, beta-Aminopropionic acid</u>
<u>Abu</u>	<u>2-Aminobutyric acid</u>
<u>4Abu</u>	<u>4-Aminobutyric acid, piperidinic acid</u>
<u>Acp</u>	<u>6-Aminocaproic acid</u>
<u>Ahe</u>	<u>2-Aminoheptanoic acid</u>
<u>Aib</u>	<u>2-Aminoisobutyric acid</u>
<u>bAib</u>	<u>3-Aminoisobutyric acid</u>
<u>Apm</u>	<u>2-Aminopimelic acid</u>
<u>Dbu</u>	<u>2,4-Diaminobutyric acid</u>
<u>Des</u>	<u>Desmosine</u>
<u>Dpm</u>	<u>2,2'-Diaminopimelic acid</u>
<u>Dpr</u>	<u>2,3-Diaminopropionic acid</u>
<u>EtGly</u>	<u>N-Ethylglycine</u>
<u>EtAsn</u>	<u>N-Ethylasparagine</u>
<u>Hyl</u>	<u>Hydroxylysine</u>
<u>aHyl</u>	<u>alo-Hydroxylysine</u>

<u>3Hyp</u>	<u>3-Hydroxyproline</u>
<u>4Hyp</u>	<u>4-Hydroxyproline</u>
<u>Ide</u>	<u>Isodesmosine</u>
<u>aIle</u>	<u>allo-Isoleucine</u>
<u>MeGly</u>	<u>N-Methylglycine, sarcosine</u>
<u>MeIle</u>	<u>N-Methylisoleucine</u>
<u>MeLys</u>	<u>6-N-Methyllysine</u>
<u>MeVal</u>	<u>N-Methylvaline</u>
<u>Nva</u>	<u>Norvaline</u>
<u>Nle</u>	<u>Norleucine</u>
<u>and</u>	
<u>Orn</u>	<u>Ornithine.</u>

77 (previously presented). The polypeptide of claim 76 where no more than one of the amino acids of said polypeptide which lie outside said sequence, if any, is a non-natural or unusual amino acid other than a D-isomer of one of the genetically encoded amino acids.

78 (previously presented). The polypeptide of claim 76 which is not more than 15 a.a. in length.

79 (previously presented). The polypeptide of claim 77 which is not more than 15 a.a. in length.

80 (previously presented). A method of preventing death due to pancreatitis which comprises administering to a subject an effective amount of a pharmaceutical composition according to claim 41.

81 (previously presented). A method of preventing development of acute respiratory-distress like syndrome which comprises administering to a subject an effective amount of a pharmaceutical composition according to claim 41.

82 (previously presented). The polypeptide of claim 18 where

$X_4$  and/or  $X_5$  are independently selected from the group

consisting of Met, Ile, Leu, Val, norvaline, norleucine, N-methylvaline, N-methyl isoleucine, allo-leucine, and their D-isomers, and

X<sub>3</sub> is L-Lys, L-Orn, or one of their D-isomers.

83 (previously presented). The method of claim 49 in which the disease is an inflammatory disease.

84 (previously presented). The method of claim 49 in which the disease is a skin disease.

85 (previously presented). The method of claim 49 in which the disease is psoriasis.

86 (previously presented). The method of claim 49 in which the disease is an auto-immune disease.

87 (previously presented). The method of claim 49 in which the disease is characterized by decreased or insufficient production, or decreased or insufficient activity, of IL-10.

88 (new). The polypeptide of claim 18 where SEQ ID NO:19 is the C-terminal of said polypeptide.

89 (new). The polypeptide of claim 18 where if the polypeptide is stabilized, the stabilization is at least in part the result of the attachment of an alpha-helical mimetic.

90 (new). The method of claim 49 in which the disease is characterized by excessive production or activity of at least one compound selected from the group consisting of IL-8, IL-1 $\beta$ , MCP-1, IFN- $\gamma$  and TNF- $\alpha$ , or by inadequate production or activity of IRAP or IL-4.

91 (new). The method of claim 49 in which the disease is ulcerative colitis.